UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/872,868	05/01/2001	Timothy Gardner	CEL-002	1090

7590 11/05/2003

Brenda Herschbach Jarrell
Choate Hall & Stewart
Exchange Place
53 State Street
Boston, MA 02109

EXAMINER	
LEFFERS JR, GERALD G	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 11/05/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/872,868	GARDNER ET AL.	
	Examin r	Art Unit	
	Gerald G Leffers Jr., PhD	1636	

-- The MAILING DATE of this communication appears on the cover sheet with th correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 August 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-30* is/are pending in the application.

4a) Of the above claim(s) *17-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-16* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Receipt is acknowledged of an amendment, filed 8/11/03, in which several claims were amended (claims 1, 10-11). Claims 1-30 are pending in the instant application, with claims 17-30 withdrawn as being directed to nonelected inventions.

Any rejection of record in the office action mailed 4/9/03 as Paper No. 13 not addressed herein is withdrawn. This action is not final as at least one new grounds of rejection is made herein that was not necessitated by applicants' amendment of the claims in the response filed 8/11/03.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 12, 15-16 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The instant specification teaches the genetic switch of the invention can be useful in human gene therapy applications. Thus, the rejected claims can reasonably be read as to encompass a human cell in a human body, or even a human. Therefore, the claims can be reasonably read to encompass nonstatutory subject matter. It would be remedial to amend the claims to clearly indicate that the claimed host cells are isolated in some fashion from their native environment (e.g. an "isolated" host cell). **This is a new rejection.**

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-7, 10-16 are rejected under 35 U.S.C. 102(b) as being anticipated by Bailey et al. (U.S. Patent No. 5,416,008 A; see the entire patent). **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 8/11/03.**

Bailey et al teach recombinant constructs and methods for the cross-regulation of gene expression in recombinant cells. Different combinations of repressors/operons are taught in which the repressors encoded by different operons regulate the transcription of the other operons (e.g. Figure 1; column 6, lines 19-29). The patent describes several repressor/operator systems that are operable in the constructs of the invention (e.g. lac, trp, λ cI, GAL10, PHO5, etc.; columns 4-5, bridging paragraphs). In particular, constructs VII-VIII of Figure 1 are each directed to a pair of operons wherein one operon encodes a repressor (R) that regulates transcription from the other operon, and the other operon encodes a repressor (R2) that regulates transcription from the first operon. Transcription from either operon can be regulated by the derepression of a given repressor (e.g. "dilution" of the repressor) or by addition of an inducer (e.g. a "switching agent such as IPTG). The operons can be located physically on either an extrachromosomal element or on a chromosome. A sequence encoding a gene of interest can be operatively linked to either operon as there is no functional distinction between either of the

operons described by constructs VII and VIII. Host cells can be prokaryotic or eukaryotic (e.g. E. coli or yeast; column 1, lines 12-15; claims 2 or 3).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 8-9 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bailey et al. (U.S. Patent No. 5,416,008 A; see the entire patent). **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 8/11/03.**

The teachings of Bailey et al are described above and are applied as before, except: Bailey et al do not explicitly teach that a fourth sequence, encoding a second gene of interest that is not a repressor, can be operatively linked to the operon that does not already comprise a

sequence encoding a protein of interest (e.g. the operon encoding R in constructs VII-VIII of Figure 1).

It would have been obvious to one of ordinary skill in the art at the time of applicants' invention to modify the systems taught by Bailey et al to include a second sequence of interest operatively linked to the operon that does not already comprise a sequence of interest because Bailey et al teach it is within the skill of the art to utilize a duel operon system to regulate the transcription of the first gene of interest encoding a structural protein and because the skilled artisan would readily recognize that the same principles for cross-regulation would work in reverse. One would have been motivated to do so in order to obtain the expected result of being able to regulate expression of more than one desired gene product and in order to obtain the second gene product in a controlled manner. Absent any evidence to the contrary, there would have been a reasonable expectation of success in utilizing a second sequence encoding a second gene product of interest in the constructs as taught by Bailey et al for the controlled expression of a second desired gene product.

Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-16 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of copending Application No. 09/872,339. Although the conflicting claims are not identical, they are not patentably distinct from each other because of the following reasons. **This is a new rejection necessitated by applicants' amendment of the claims in the response filed 8/11/03.**

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

The instant claims are directed to a duel operon system in which the promoters of each operon are regulated by repressor proteins that are encoded by the other operon, resulting in a genetic toggle switch that is regulatable by the absence/presence of the two repressors. The first repressor, encoded by the first operon, is necessarily inducible by an activating agent (e.g. an inducer such as IPTG). The second repressor, encoded by the second operon is necessarily capable of regulating transcription from the first promoter, which is itself necessarily an inducible promoter. Each of the promoters is inducible by the addition of a switching agent. The first and second constructs can further comprise additional sequences encoding a gene or genes of interest. The claims are also directed to eukaryotic and prokaryotic host cells comprising the duel constructs (e.g. E. coli or yeast).

The claims of the 09/872,339 application are also directed to a duel construct expression system (termed an adjustable threshold genetic switch). In this case, the first and second promoters are active in the absence of a repressor, but only the first promoter is necessarily

inducible by the addition of a switching agent. The other promoter, while regulated by a repressor, is not necessarily derepressed in response to a switching agent (e.g. it could be regulated by the temperature sensitive cI857 repressor).

In practicing the methods of the '339 application, one would be motivated to determine from the specification the types of promoter/repressor combinations that are usable in the invention. The '339 application teaches that the repressors of the invention can be regulated by "switching agents" (e.g. arabinose, IPTG, etc.) or by repressors that are responsive to some other environmental cue (e.g. the temperature sensitive cI857 repressor). Therefore, it would have been obvious to practice the claimed invention of the '339 application with both promoter/operator pairs responsive to switching agents because repressors responsive to such agents are exemplified in the specification.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gerald G Leffers Jr., PhD whose telephone number is (703) 308-6232. The examiner can normally be reached on 9:30am-6:00pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Remy Yucel can be reached on (703) 305-1998. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Gerald G Leffers Jr., PhD
Primary Examiner
Art Unit 1636

Ggl

GERRY LEFFERS
PRIMARY EXAMINER